The Impact of Physical Activity on Brain Structure and Function in Youth: A Systematic Review

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abstract

CONTEXT: Advances in neuroimaging techniques have resulted in an exponential increase in the number of studies investigating the effects of physical activity on brain structure and function. Authors of studies have linked physical activity and fitness with brain regions and networks integral to cognitive function and scholastic performance in children and adolescents but findings have not been synthesized.

OBJECTIVE: To conduct a systematic review of studies in which the impact of physical activity on brain structure and function in children and adolescents is examined.

DATA SOURCES: Six electronic databases (PubMed, PsychINFO, Scopus, Ovid Medline, SportDiscus, and Embase) were systematically searched for experimental studies published between 2002 and March 1, 2019.

STUDY SELECTION: Two reviewers independently screened studies for inclusion according to predetermined criteria.

DATA EXTRACTION: Two reviewers independently extracted data for key variables and synthesized findings qualitatively.

RESULTS: Nine studies were included (task-based functional MRI [n = 4], diffusion tensor imaging [n = 3], arterial spin labeling [n = 1], and resting-state functional MRI [n = 1]) in which results for 5 distinct and 4 similar study samples aged 8.7 ± 0.6 to 10.2 ± 1.0 years and typically of relatively low socioeconomic status were reported. Effects were reported for 12 regions, including frontal lobe (n = 3), parietal lobe (n = 3), anterior cingulate cortex (n = 2), hippocampus (n = 1), and several white matter tracts and functional networks.

LIMITATIONS: Findings need to be interpreted with caution as quantitative syntheses were not possible because of study heterogeneity.

CONCLUSIONS: There is evidence from randomized controlled trials that participation in physical activity may modify white matter integrity and activation of regions key to cognitive processes. Additional larger hypothesis-driven studies are needed to replicate findings.

Many children and adolescents are not sufficiently active to accrue the extensive cardiovascular, metabolic, musculoskeletal, and mental health benefits of physical activity. Habitual physical activity is associated with a variety of health-related fitness traits (ie, cardiorespiratory, morphologic, muscular, motor, and metabolic), and emerging evidence suggests that participation in physical activity and improving physical fitness may enhance cognitive health across the life span.

Specifically, acute physical activity can enhance children’s attention ($g = 0.43$; 95% confidence interval [CI] = 0.09–0.77) and on-task behavior in the classroom ($d = 0.77$; 95% CI = 0.22–1.32). Similarly, authors of experimental studies have demonstrated longer-term benefits of physical activity for executive functions ($g = 0.24$; 95% CI = 0.09–0.39), attention ($g = 0.90$; 95% CI = 0.56–1.24), and academic performance ($g = 0.26$; 95% CI = 0.02–0.49). Higher levels of cardiorespiratory fitness are also positively associated with young people’s academic achievement. Although awareness of the positive effects of physical activity on cognitive and/or academic outcomes has increased rapidly in the last 5 years, the mechanisms responsible remain relatively untested in young people.

Animal studies have provided initial insight into the neurobiological changes induced by physical activity. Molecular effects include epigenetic regulation of gene expression and related changes in concentrations of factors such as brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor, known to underpin brain plasticity and cellular changes such as neurogenesis, synaptogenesis, and angiogenesis. There is now empirical evidence that the same molecular effects exist in humans (eg, increases in BDNF and vascular endothelial growth factor) and may be responsible for the positive effects of physical activity on cognitive health.

In addition, a seminal randomized controlled trial (RCT) in older adults demonstrated that 12 months of aerobic exercise increased hippocampal volume and improved memory, with these improvements being mediated by increases in BDNF. Since the publication of these findings, there has been an exponential increase in the number of studies employing MRI techniques to examine associations and explore the impact of physical activity on brain structure and function in humans.

Authors of many cross-sectional studies have linked physical activity with brain regions and networks integral to cognitive function and scholastic performance in children and adolescents. To date, there has been no systematic review of experimental MRI studies in which the impact of physical activity on brain structure and function in children and adolescents is investigated. A recent review of 84 studies in which the effects of physical activity on cognitive functioning and neuroimaging findings were investigated only included 5 MRI studies because the search was conducted in July 2017 and it only included RCTs. To provide a more in-depth and up-to-date summary of evidence of MRI studies specifically, our review included all designs of experimental studies. Given the importance of cognitive development, clarifying the effects of physical activity on brain structure and function may motivate key stakeholders to address the current physical inactivity pandemic. Therefore, our aim with this study was to conduct a systematic review of MRI studies in which the impact of physical activity on brain structure and function in school-aged children have been examined.

**METHODS**

The conduct and reporting of this review adhere to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. The review protocol was registered with the International Prospective Register of Systematic Reviews (CRD42017081804).

**Study Eligibility Criteria**

1. **Types of participants:** participants were typically developing school-aged children (usually 5–18 years of age; however, children outside this age range were included if they were recruited within schools). Studies including populations with learning difficulties, cognitive deficits, and developmental disorders were excluded.

2. **Types of studies:** experimental studies were eligible if the authors reported statistical analyses of changes in brain structure or function before and after a physical activity intervention.

3. **Measure of physical activity, cardiorespiratory fitness, or muscular fitness:** studies with objective (eg, accelerometers and pedometers) or subjective measures of physical activity (eg, exercise session attendance and self-report questionnaires); cardiorespiratory fitness (eg, maximum oxygen consumption [VO$_{\text{max}}$] test, Progressive Aerobic Cardiovascular Endurance Run, and predictive equations); and/or muscular fitness (eg, dynamometry, standing long jump, and push up test) were eligible.

4. **Brain imaging techniques:** studies that reported findings from MRI techniques (eg, functional MRI [fMRI], diffusion tensor imaging [DTI], and arterial spin labeling [ASL]) that have been used to identify structural and functional
mechanisms that may explain the relationship between physical activity, cardiorespiratory fitness or muscular fitness, and cognition or academic achievement were eligible.

Information Sources and Search Strategy
Six electronic databases (PubMed, PsychINFO, Scopus, Ovid Medline, SportDiscus, and Embase) were searched for studies published within the last 16 years (2002–March 1, 2019) (Supplemental Table 4). Additional searches of recently published systematic reviews in which the associations between physical activity, cardiorespiratory fitness or muscular fitness, and cognitive outcomes were examined were conducted, and the reference lists of all retrieved studies were reviewed. The search was restricted to articles published in the English language.

Study Selection
The study screening and selection process was performed on Covidence. One reviewer screened the titles and abstracts of records retrieved by the search strategy and classified these as possibly relevant or definitely irrelevant. The full-text articles of records classified as possibly relevant were retrieved and independently reviewed by 2 reviewers. Studies were classified as include or exclude. If there was disagreement between reviewers, consensus was sought through discussion. Reasons were provided for excluding any possibly relevant studies.

Data Extraction
Both reviewers independently extracted data from included studies into a purpose-built data extraction template in excel. Data extraction included (1) sample data (including sample size, age, sex, and education); (2) study details (location, design, setting, duration, and assessment points); (3) assessment of physical activity, cardiorespiratory, and/or muscular fitness (objective, subjective, laboratory-based, or field-based); (4) neuroimaging data (MRI modality, analysis methods, regions of interest, etc); (5) data analysis (statistical methods used, confounders adjusted for, etc); and (6) study findings (quantitative and qualitative).

Risk of Bias Assessment
All studies were independently assessed by 2 reviewers and were scored as low, high, or unclear for 8 criteria according to the Cochrane collaboration risk of bias tool and scoring. Any disagreement concerning risk of bias assessment between the 2 reviewers was resolved through discussion. Consensus was reached on all articles included in the review.

RESULTS
Overview of Studies
Figure 1 displays the flow of studies through the review process. After the exclusion of duplicates, the systematic search yielded 9508 potentially relevant citations, of which 153 were retained for full-text review. There was almost-perfect interrater agreement for the full-text review (κ = 0.97). A total of 9 articles satisfied the inclusion criteria and were included in the review, reporting results for 5 distinct and 4 similar samples of participants ranging from 8.7 ± 0.6 to 10.2 ± 1.0 years of age and typically of relatively low socioeconomic status. The sample size ranged from 9 to 143. The studies were conducted in North America (8 in the United States) and Asia (1 in China). Of the included studies, 7 were RCTs and 2 were acute before and after studies. Detailed information about each included study is presented in Table 1.

Risk of Bias
Detailed information about the risk of bias for the included studies is presented in Table 2. In summary, all 9 (100%) were deemed to be at unclear risk of selection bias, with unclear description of (1) sequence generation process, (2) concealed allocation processes, and [in 5 (56%) studies] (3) subgroup selection processes. Seven (78%) studies were deemed at unclear risk of reporting bias because of lack of availability of a protocol published by means of either an article or trial registration. Six (67%) studies were deemed at high risk of attrition bias because of significant dropout with inadequate analyses. Overall, only 2 (22%) studies scored as low risk of bias for ≥3 of the 8 criteria. There was substantial interrater agreement for the risk of bias assessment (κ = 0.61).

Measures of Brain Structure and Function
Four different MRI modalities were used across the 9 included studies. Four (44%) studies used task-based fMRI, 3 (33%) studies used DTI, 1 (11%) study used ASL, and 1 (11%) study used resting-state fMRI. Data for 12 regions were reported across the 9 included studies: anterior cingulate cortex, cerebellum, corpus callosum, frontal lobe, hippocampus, parietal lobe, superior longitudinal fasciculus, uncinate fasciculus, cognitive control network, default mode network, executive control network, and motor network.

Measures of Physical Activity and Fitness
Authors of seven (78%) studies provided physical activity interventions and investigated effects on brain structure or function. The duration of the interventions ranged from 3 to 9 months and generally consisted of moderate-to-vigorous physical activity (eg, 70%–80% maximum heart rate.
HR_{\text{max}}) either twice a week or each school day for 20 to 120 minutes. Of these, 4 studies measured cardiorespiratory fitness by means of oxygen uptake during a maximal graded treadmill test (modified Balke protocol).\textsuperscript{34,37,39,42} Authors of 2 studies investigated changes in brain function in response to acute bouts of aerobic exercise at 60% to 70% HR_{\text{max}}.\textsuperscript{35,36} Details of all interventions are outlined in Table 1.

The Impact of Physical Activity on Brain Structure or Function

Findings from each included study are presented by brain region below and Table 1, with effects further summarized in Table 3.

**Frontal Lobe**

Authors of 3 RCTs with distinct but similarly aged samples reported results for changes in activation of the frontal lobe in response to physical activity interventions which ranged from 20 to 77 minutes each school day over 3 to 9 months. Authors of 2 of the RCTs assessed prefrontal activation during cognitive tasks (antisaccade \(n = 2\) and flanker \(n = 2\)) and found changes pre- and post- intervention but the effects were in opposite directions in both cases. Davis et al\textsuperscript{38} reported that increased bilateral prefrontal (and decreased posterior parietal) cortex activity was observed during antisaccade performance in the physical activity group, whereas Krafft et al\textsuperscript{39} reported decreased activation during antisaccade performance in several prefrontal (and parietal) regions including medial frontal gyrus, right inferior frontal gyrus, and bilateral precentral gyrus. Krafft et al\textsuperscript{39} also observed increased activation of the superior frontal gyrus of the prefrontal cortex during incongruent trials of the flanker task in the physical activity group, whereas authors of the third RCT (Chaddock-Heyman et al\textsuperscript{37}) observed decreased activation in the right anterior prefrontal cortex during incongruent trials of the flanker task in the physical activity intervention group but no changes in the control group. Note that although both Chaddock-Heyman et al\textsuperscript{37} and Davis et al\textsuperscript{38} adjusted for baseline during their region of interest analyses, Krafft et al\textsuperscript{39} did not report if/what covariates were adjusted for and employed a whole-brain analysis approach, which could contribute to the disparate results.

**Parietal Lobe**

Authors of 3 studies reported results for the parietal lobe from task-based fMRI paradigms. Authors of 2 RCTs with similarly aged samples and relatively similar type, frequency, intensity, and duration of physical activity interventions found decreased parietal cortex activity during antisaccade performance after a physical activity intervention.\textsuperscript{38,39} Both studies used comparable cluster size thresholds but it should be noted that while Davis et al\textsuperscript{38} adjusted for baseline in their analyses, Krafft et al\textsuperscript{39} did not report if and what covariates were adjusted for.

Chen et al\textsuperscript{36} investigated the acute effects of a 30-minute bout of cycling (60%–69% HR_{\text{max}}) during task-based fMRI and reported improved n-back performance and increased activation of bilateral parietal cortices (as well as the left hippocampus and bilateral cerebellum).

**Anterior Cingulate Cortex**

Authors of 2 RCTs reported task-based fMRI results for the anterior cingulate cortex. Authors of 1 RCT found that participation in a physical activity intervention did not change activation of anterior cingulate cortex during neutral or incongruent conditions of a flanker task.\textsuperscript{37} The other RCT found that although there

FIGURE 1
Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram.
<table>
<thead>
<tr>
<th>First Author and Year</th>
<th>Study and Sample Characteristics (Design, n, Age (y), ±, % Male Sex, SES, Country)</th>
<th>Exposure</th>
<th>Measure of Physical Activity and/or Fitness</th>
<th>Imaging Technique and Analysis</th>
<th>Confounders Adjusted for in Analyses</th>
<th>Key Findings</th>
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</thead>
<tbody>
<tr>
<td>Frontal lobe: executive processes, cognition, attention, and language processing</td>
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<tr>
<td>Chaddock-Heyman et al 2013</td>
<td>RCT, 23, 83 ± 83, 71, 20 ± 0.5 United States</td>
<td>2 h (76.8 min MVPA) aerobic and muscle- and/or bone-strengthening activities after each school day for 150 out of 170 school days. Mean (SD) attendance = 82% ± 13.3%</td>
<td>VO_{2\text{peak}} (modified Balke)</td>
<td>Task-based fMRI: FSL, ROI approach, motion correction via a rigid body algorithm in MOCART. Primary threshold level input (z): 6.00; corrected cluster significance threshold: P &lt; .05; familywise α level: P &lt; .05</td>
<td>Baseline</td>
<td>Intervention participants showed decreases in fMRI brain activation in the right anterior prefrontal cortex (Z = 6.2) during a flanker task</td>
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<td>Davis et al.</td>
<td>RCT, 19, 98 ± 10, 58, not reported, United States</td>
<td>Daily afterschool exercise program including running games, jump rope, and modified basketball and soccer at 166 ± 8 beats per minute (~79% HR_{max}) 20–40 min/d for 14 ± 1.7 wk. Mean attendance = 85% ± 13%</td>
<td>HR monitors and attendance</td>
<td>Task-based fMRI: AFNI and ROI approach. Volumes were registered to a representative volume, and 6 regressors were calculated (rotational and translational head motion in 3 planes). Monte Carlo simulations threshold-cluster method familywise α at P &lt; .05 preserved with individual voxel threshold at P &lt; .05 and a cluster size of 40 voxels</td>
<td>Baseline</td>
<td>Increased prefrontal (and decreased posterior parietal) cortex activity during antisaccade performance was observed in the exercise group</td>
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<td>Kraft et al.</td>
<td>RCT, 43, 98 ± 80, 35, 49 ± 1.1 United States</td>
<td>8 mo instructor-led afterschool intervention (eg, tag and jump rope) 40 min each school day at 161 beats per minute (mean; ~77% age-predicted HR_{max})</td>
<td>VO_{2\text{peak}} (modified Balke)</td>
<td>Task-based fMRI: AFNI, whole-brain approach. Volumes were registered to a representative volume and regressed for rotation in x, y, and z planes. Monte Carlo simulations threshold-cluster method: familywise α of .05 preserved with 3D cluster size of 35 (antisaccade) or 37 (flanker) voxels.</td>
<td>Not reported</td>
<td>Exercise led to decreased activation in several prefrontal (and parietal) regions supporting antisaccade performance, including bilateral precentral gyrus, medial frontal gyrus, paracentral lobule, and right inferior frontal gyrus. The exercise group also showed increased activation in several regions supporting flanker performance, including superior frontal gyrus and the anterior cingulate</td>
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<td>Parietal lobe: perception and integration of somatosensory information</td>
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<tr>
<td>Chen et al.</td>
<td>Acute before and after, 9, 10, 56, not reported, China</td>
<td>30 min cycling at 60%–69% age-predicted HR_{max}</td>
<td>HR monitors</td>
<td>Task-based fMRI: SPM8, whole-brain approach, motion corrected. Statistical threshold: P &lt; .025; cluster size threshold = 100 voxels.</td>
<td>Baseline</td>
<td>Acute moderate-intensity aerobic exercise benefited performance in the n-back task, increasing brain activities of the left parietal cortex (T = 8.64), right parietal cortex (T = 8.64) during a flanker task</td>
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<td>Davis et al 2011</td>
<td>RCT, 19.9 ± 10.58, not reported, United States</td>
<td>Daily afterschool exercise program including running games, jump rope, and modified basketball and soccer at 166 ± 8 beats per minute (~79% HR_{max}) for 20–40 min/d for 14 ± 1.7 wk. Mean attendance = 85% ± 13%</td>
<td>HR monitors and attendance</td>
<td>Equivalent to cluster-level P &lt; .05. AlphaSim corrected</td>
<td>Baseline</td>
<td>Decreased posterior parietal cortex (and increased prefrontal cortex) activity during antisaccade performance was observed in the exercise group</td>
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<td>Krafft et al 2014</td>
<td>RCT, 38.8 ± 8.8, 40.7 ± 1.2, United States</td>
<td>Instructor-led afterschool intervention (eg, tag and jump rope) 40 min daily at 161 beats per minute (mean: ~77% age-predicted HR_{max})</td>
<td>VO_{peak} (modified Balke)</td>
<td>Task-based fMRI: AFNI, ROI approach. Volumes were registered to a representative volume, and 6 regressors were calculated (rotational and translational head motion in 3 planes). Monte Carlo simulations threshold-cluster method familywise α at P = .05, preserved with individual voxel threshold at P = .05 and a cluster size of 40 voxels</td>
<td>Not reported</td>
<td>Exercise led to decreased activation in several parietal (and prefrontal) regions supporting antisaccade performance, including superior parietal lobule, inferior parietal lobule, paracentral lobule, postcentral gyrus, and left precuneus</td>
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<td>Chaddock-Heyman et al 2013</td>
<td>RCT, 23, 8.9 ± 5.8, 71.2 ± 0.9, United States</td>
<td>2 h (78.9 min MVPA) aerobic and muscle- and/or bone-strengthening activities after each school day for 150 out of 170 school days. Mean (SD) attendance = 82% ± 13%</td>
<td>VO_{peak} (modified Balke)</td>
<td>Task-based fMRI: FSL, ROI approach. Motion correction via a rigid body algorithm in MFLUR. Primary threshold level input (A &gt; 600; corrected cluster significance threshold: P &lt; .05; familywise α level: P = .05</td>
<td>Baseline</td>
<td>Intervention participants showed no changes in fMRI brain activation of the anterior cingulate cortex (z = 7.1) during a flanker task</td>
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<td>Krafft et al 2014</td>
<td>RCT, 43, 9.8 ± 0.8, 35.4 ± 1.1, United States</td>
<td>Instructor-led after school intervention (eg, tag and jump rope) 40 min daily at 161 beats per minute (mean: ~77% age-predicted HR_{max})</td>
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<td>Task-based fMRI: AFNI, whole-brain approach. Volumes were registered to a representative volume and regressed for rotation in x, y, &amp; z planes. Monte Carlo simulations threshold-cluster method: familywise α of .05 preserved with 3D cluster size of 35 (antisaccade) or 37 (flanker) voxels</td>
<td>Not reported</td>
<td>Exercise led to decreased activation in the anterior cingulate cortex (as well as the several prefrontal and parietal regions) during antisaccade performance. The exercise group also showed increased activation in several regions supporting flanker performance, including the anterior cingulate and superior frontal gyrus</td>
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Key: RCT = randomized controlled trial; VO_{peak} = peak oxygen consumption; HR_{max} = maximum heart rate; O/E = observed-to-expected ratio; MCFLIRT = multiple regression of linear contrasts; AlphaSim = method for assessing the statistical significance of clusters of images; Familywise = familywise error rate; P = probability; ROI = region of interest; AFNI = analysis of functional neuroimages; FSL = FMRIB's software library; MVPA = moderate to vigorous physical activity; SD = standard deviation; % = percentage; SES = socioeconomic status; y = years; wk = weeks; min = minutes; beat = beats; min/d = minutes per day; fl = flanker; Balanced = balanced design; HRmax = maximum heart rate.
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<td><strong>Hippocampus:</strong> memory and spatial navigation</td>
<td>Chen et al 2016&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Acute before and after, 9, 10, 56, not reported, China</td>
<td>30 min cycling at 60%–69% age-predicted $HR_{\text{max}}$</td>
<td>HR monitors</td>
<td>Task-based fMRI. SPM8, whole-brain approach, motion corrected. Baseline</td>
<td>Acute moderate-intensity aerobic exercise benefited performance in the n-back task, increasing brain activities of the left parietal cortex ($T = 8.64$), right parietal cortex ($T = 6.57$), left hippocampus ($T = 8.23$), left cerebellum ($T = 7.18$), and right cerebellum ($T = 6.47$)</td>
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<td><strong>Cerebellum:</strong> coordination of voluntary movement, motor learning, balance, and sequence learning</td>
<td>Chen et al 2016&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Acute before and after, 9, 10, 56, not reported, China</td>
<td>30 min cycling at 60%–69% age-predicted $HR_{\text{max}}$</td>
<td>HR monitors</td>
<td>Task-based fMRI. SPM8, whole-brain approach. Statistical threshold: $P &lt; .025$; cluster size threshold = 100 voxels, equivalent to cluster-level $P &lt; .05$. AlphaSim corrected</td>
<td>Acute moderate-intensity aerobic exercise benefited performance in the n-back task, increasing brain activities of the left parietal cortex ($T = 8.64$), right parietal cortex ($T = 6.57$), left hippocampus ($T = 8.23$), left cerebellum ($T = 7.18$), and right cerebellum ($T = 6.47$)</td>
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<td><strong>Functional Networks</strong></td>
<td>Krafft et al 2014&lt;sup&gt;40&lt;/sup&gt;</td>
<td>RCT, 22, 95 ± 0.7, 32, 4.6 ± 12.6 United States</td>
<td>8 mo instructor-led afterschool intervention (eg, tag and jump rope) 40 min each school day at 194 beats per minute (mean; ~78% age-predicted $HR_{\text{max}}$)</td>
<td>HR monitors</td>
<td>Resting-state fMRI. FSL, ICA approach. Visually inspected for absolute motion &gt;1 mm shift, components representing noise were removed, and 6 motion time courses (estimated rotation and shift in x, y, and z planes) were removed. Uncorrected voxel threshold = $P &lt; .0001$. Familywise $\alpha$ of .05 preserved with 3D clusters of $\geq 169$ voxels</td>
<td>Results showed a pattern of decreased synchrony after exercise training with 3 RSNs (default mode network, cognitive control, and motor). Although the motor network showed decreased synchrony in the exercise group with the cuneus, the motor network was the only RSN to also show an opposing pattern of increased synchrony within the exercise group.</td>
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<td>Pontifex et al 2018&lt;sup&gt;55&lt;/sup&gt;</td>
<td>Acute crossover, 41, 10.2 ± 10, 56, 0.8 ± 0.2 United States</td>
<td>20 min fast walk and slow jog on a treadmill at 70% age-predicted $HR_{\text{max}}$</td>
<td>HR monitors</td>
<td>ASL, AFNI and FSL whole-brain and ROI approaches. Control-label perfusion weighted difference images were linearly aligned to proton-density weighted images and None (no correlation between change in CBF and age, sex, pubertal status, IQ, or change in HR or blood pressure)</td>
<td>Findings revealed no differences in CBF after the cessation of exercise relative to the active control condition across each of the networks examined (frontoparietal, executive control, and motor).</td>
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<td>White matter integrity</td>
<td>Chaddock-Heyman et al 2018</td>
<td>RCT, 143, 8.7 ± 0.55, 48, 1.91 ± 0.78&lt;sup&gt;a&lt;/sup&gt; United States</td>
<td>2 h after each school day for 150 d of the 170-d school year. There was 30–35 min of sustained MVPA and 90 min of intermittent MVPA</td>
<td>VO&lt;sub&gt;2&lt;/sub&gt;max (modified Balke), HR monitors, and accelerometers</td>
<td>Not reported (no baseline group differences for age, sex, race, IQ, SES, pubertal timing, VO&lt;sub&gt;2&lt;/sub&gt;peak, and BMI)</td>
<td>PA group had increased FA and decreased RD in the genu of the corpus callosum from pre- to post-test, with no changes in axonal fiber diameter. No changes in WMI in the waitlist control group.</td>
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<td>Krafft et al 2014&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RCT, 18, 9.7 ± 0.7, 50, 4.6 ± 12&lt;sup&gt;b&lt;/sup&gt; United States</td>
<td>8 mo instructor-led afterschool intervention (e.g., tag and jump rope) 40 min each school day at 161 beats per minute (mean; ~77% age-predicted HR&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>DTI: FSL and Explore DTI; ROI approach. Visual inspection for and removal of motion-distorted volumes; eddy current corrected. Thresholding was not reported</td>
<td>Age and sex</td>
<td>Intervention did not increase SLF WMI, but higher attendance at exercise sessions, higher intensity, and greater total dose of exercise were all associated with increased SLF WMI (increased FA and decreased RD) in a dose-response manner.</td>
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<td>Schaeffer et al 2014&lt;sup&gt;c&lt;/sup&gt;</td>
<td>RCT, 18, 9.7 ± 0.7, not reported, not reported, United States</td>
<td>8 mo of 40 min of instructor-led aerobic activities (e.g., tag or jump rope) every school day. Mean (SD) attendance = 60 (30%), HR = 161 (8) beats per minute, intensity = 63 (1.6) METs</td>
<td>DTI: FSL and Explore DTI; ROI approach. Visual inspection for and removal of motion-distorted volumes; eddy current corrected. Thresholding was not reported</td>
<td>Race and sex</td>
<td>The exercise group showed significantly greater positive change in bilateral uncinate FA than the sedentary group. The exercise group also showed a greater negative change in left uncinate fasciculus RD.</td>
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</table>

AFNI, Analysis of Functional Neuroimages; CBF, cerebral blood flow; FA, fractional anisotropy; FDT, functional MRI of the Brain’s Diffusion Toolbox; FSL, functional MRI of the Brain Software Library; HR, heart rate; HR<sub>max</sub>, maximum heart rate; ICA, independent component analysis; MCFLIRT, Motion Correction functional MRI of the Brain’s Linear Image Registration Tool; MVPA, moderate-to-vigorous physical activity; PA, physical activity; RD, radial diffusivity; RDI, region of interest; RSN, resting-state network; SES, socioeconomic status; SLF, superior longitudinal fasciculus; SPM8, Statistical Parametric Mapping 8; TBSS, Tract-Based Spatial Statistics; VO<sub>2</sub>peak, peak oxygen consumption; WMI, white matter integrity; 3D, three-dimensional.

<sup>a</sup> Low: <2.

<sup>b</sup> Parental education scale (1 = grade 7 or less; 2 = grades 8–9; 3 = grades 10–11; 4 = high school graduate; 5 = partial college; 6 = college graduate; 7 = postgraduate).
were no significant correlations between changes in cardiorespiratory fitness and brain activation during task-based fMRI, the physical activity intervention led to differential activation across 2 inhibition tasks, with decreased activation of the anterior cingulate cortex during an antisaccade task and increased activation of the cingulate gyrus during the incongruent condition of a flanker task. Comparatively, the control group showed decreased activation during the flanker task. Such differences across inhibition tasks highlights the complexity of brain activation during performance of tasks that tap different aspects of a similar cognitive construct.

Hippocampus
Authors of 1 acute before and after study reported enhanced performance in an n-back task and increased brain activity (task-based fMRI) of the left hippocampus in response to an acute 30-minute bout of cycling (60%–69% HR_max).

Cerebellum
Authors of 1 acute experimental study investigated the effects of a 30-minute bout of cycling (60%–69% HR_max) during task-based fMRI and reported improved n-back performance and increased activation of bilateral cerebellum.

Functional Networks
Authors of 2 experimental studies reported results for specific functional brain networks. Authors of 1 RCT used an independent component analysis approach and reported that a physical activity intervention caused decreased synchrony between the default mode network and the cognitive control network with brain regions outside of those networks during resting-state fMRI. There was no change in synchrony of the salience network, whereas the motor network had decreased synchrony with the left cuneus but increased synchrony with certain frontal regions.

### TABLE 2 Risk of Bias Assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Sequence Generation</th>
<th>Allocation Concealment</th>
<th>Participant Blinding</th>
<th>Assessor Blinding</th>
<th>Personnel Blinding</th>
<th>Selective Outcome Reporting</th>
<th>Incomplete Outcome Data</th>
<th>Other Sources of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Davis et al</td>
<td>?</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Krafft et al</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Krafft et al</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Krafft et al</td>
<td>?</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pontifex et al</td>
<td>?</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Schaeffer et al</td>
<td>?</td>
<td>?</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

+ represents low risk of bias, ? represents unclear risk of bias, and – represents high risk of bias.

a Unclear description in article.
b Significant dropout with inadequate analyses.
c Authors appeared to provide intervention and control.
d No protocol.
e Inadequate description of subgroup selection.
f Risk of intervention contamination.

### TABLE 3 Summary of Studies Which Have Examined the Impact of Physical Activity on Brain Structure or Brain Function

<table>
<thead>
<tr>
<th>Task-based fMRI</th>
<th>Positively Associated With PA</th>
<th>Negatively Associated With PA</th>
<th>Not Associated With PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task-positive regions</td>
<td>Chen et al^36,a</td>
<td>Krafft et al^39,b</td>
<td>Chaddock-Heyman et al^37</td>
</tr>
<tr>
<td></td>
<td>Davis et al^38,b</td>
<td>Krafft et al^39,a</td>
<td></td>
</tr>
<tr>
<td>Task-negative regions</td>
<td>–</td>
<td>Davis et al^38,b</td>
<td>–</td>
</tr>
<tr>
<td>Resting-state fMRI</td>
<td>–</td>
<td>Krafft et al^39,a</td>
<td>–</td>
</tr>
<tr>
<td>DTI</td>
<td>Chaddock-Heyman et al^34,d</td>
<td>Krafft et al^40,c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schaeffer et al^42,d</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>ASL</td>
<td>–</td>
<td>–</td>
<td>Pontifex et al^35</td>
</tr>
</tbody>
</table>

PA, physical activity; –, not applicable.
a Increased activation.
b Decreased activation.
c Decreased synchrony of resting-state networks with regions outside those networks.
d Increased white matter integrity.
Pontifex et al.\textsuperscript{35} investigated the acute effects of a 20-minute bout of fast walking and/or slow jogging (70% HRmax) on cerebral blood flow in 10.2 ± 1.0 year old (n = 41) and found no differences across any of the networks examined (frontoparietal, executive control, and motor networks).

**White Matter Integrity**

Authors of 3 studies reported results of 2 RCTs that had examined the effects of physical activity on white matter tracts in similarly aged children using regions of interest analyses.\textsuperscript{34,41,42} One large RCT (n = 143) revealed that 2 hours of physical activity each school day for 8 months improved white matter integrity (ie, increased fractional anisotropy, which indicates the orientation of diffusion and is higher along well-defined pathways) and decreased radial diffusivity (a marker of myelin disintegration) in the genu of the corpus callosum from pretest to post-test, with no changes in estimates of axonal fiber diameter (axial diffusivity).\textsuperscript{34} There were no changes in the white matter integrity of the wait list control group, reflective of typical development. The other RCT (n = 18) also delivered an 8-month intervention consisting of a 40-minute session each school day. Authors of 1 study reported that the physical activity group showed greater increases in bilateral uncinate fasciculus fractional anisotropy and greater decreases in left uncinate fasciculus radial diffusivity compared with the control group.\textsuperscript{42} In the second report from this RCT, the physical activity intervention did not significantly increase white matter integrity in the superior longitudinal fasciculus. However, higher attendance in the exercise intervention, higher intensity, and greater total dose of exercise were all associated with increased fractional anisotropy and decreased radial diffusivity of the superior longitudinal fasciculus in a dose-response manner.\textsuperscript{41}

**DISCUSSION**

In this systematic review, we examined evidence of the impact of physical activity on brain structure and function in youth from MRI studies. Nine experimental studies were included in the review, of which 7 were RCTs and 2 were acute before and after studies, reporting data for 12 regions acquired with 4 MRI modalities. All 7 RCT studies (4 samples) reported significant changes in either brain structure or function after a physical activity intervention in young people.\textsuperscript{37–42}

To date, the parietal cortex is the only specific region that has had >1 RCT report in which authors found an impact of physical activity on brain structure or function and for the effects to be in the same direction (ie, authors of both RCTs found decreased posterior parietal cortex activity during antisaccade performance after a physical activity intervention\textsuperscript{38,39}). Otherwise, RCT findings for the impact of physical activity on activation during task-based fMRI were inconsistent (ie, authors of 1 study found an association and another did not) for the anterior cingulate cortex,\textsuperscript{37,39} or conflicting (ie, physical activity had an impact on activation, but authors of 1 study reported increased activation and authors of another study reported a decreased activation in the case of each task paradigm [antisaccade and incongruent condition of a flanker task]) for frontal regions.\textsuperscript{37–39} It should be noted that although the sample ages and cluster size thresholds were similar in these studies, the interventions varied from 20 to 77 minutes per session over 3 to 9 months which presents considerable heterogeneity.

The desired direction of the effect of physical activity on activation will differ depending on the region and context (eg, task and rest) of interest. However, positive associations between physical activity and activation of task-positive regions during performance of task paradigms is interpreted as a greater ability to use resources in some studies,\textsuperscript{36,43,44} whereas negative associations (ie, less activation) are considered to represent a more efficient use of resources in others.\textsuperscript{37,45} There is evidence to support decreased activation of a task-positive region during task performance being reflective of a more mature and adult-like brain\textsuperscript{46–48} but this should be interpreted with caution until the findings have been replicated by studies adequately powered to perform mediation analyses.\textsuperscript{49}

Authors of 2 RCTs found that physical activity caused decreased activation of the posterior parietal cortex during antisaccade task performance. Although this did not reflect a difference in antisaccade performance between the physical activity and control group in 1 study,\textsuperscript{49} authors of the other study did not report data for antisaccade task performance.\textsuperscript{38} The inferior parietal lobule, located within the posterior parietal cortex, forms part of the default mode (task-negative) network,\textsuperscript{50–52} which is known to decouple from the cognitive control network during successful performance of a cognitive task.\textsuperscript{53} Therefore, these results may indicate a more refined, adult-like pattern of activation in the exercise group while maintaining equivalent levels of task performance.\textsuperscript{54–56} A recent meta-analysis revealed that deactivation of the default mode network is essential for processing information so that it can later be remembered.\textsuperscript{57} This diversion of processing resources from the default mode network to brain regions involved in the task performance has previously been
demonstrated in a cross-sectional pediatric physical activity study. Despite similar memory performance to their inactive peers, during encoding of later remembered versus forgotten word pairs, participants with high levels of physical activity displayed (1) robust deactivation of the default mode network, (2) strong negative coupling with the hippocampus, and (3) a more focal increase in activation of the left hippocampus only.45

Decreased synchrony between a given network and regions outside of that network is usually an indication of a more focal, coherent, and specialized pattern of activation.58,59 Authors of 1 RCT in this review examined deactivation and activation of functional networks during resting-state fMRI and found that physical activity may be conducive of a more mature efficient brain by causing decreased synchrony of the default mode network and cognitive control network with brain regions outside of those networks during resting-state fMRI.40

In terms of structural changes, 1 large RCT (FITKids2; n = 143) revealed that participation in physical activity can improve white matter integrity of the corpus callosum; a region important for cognitive processing.34 A second RCT investigated effects of physical activity on white matter integrity and detected significant improvements in the bilateral uncinate fasciculus (which usually matures later than many other tracts).42 This was particularly evident in the left uncinate fasciculus, which is linked with auditory-verbal memory proficiency, verbal IQ, and full-scale IQ.42,61,62

In a second study from the same RCT,41 changes in white matter integrity of the superior longitudinal fasciculus were not significantly different between the groups. However, higher attendance at exercise sessions, higher intensity, and greater total dose of exercise were positively associated with changes white matter integrity.31 Similarly, white matter integrity did not change among adults participating in a 1-year exercise intervention, but changes in fitness were positively associated with white matter integrity of prefrontal and temporal regions (which are linked by the uncinate fasciculus).63 Improvements in fitness were also associated with changes in short-term memory, but increases in white matter integrity were not associated with short-term memory improvement. In another larger-scale study involving adults, white matter integrity in multiple tracts (including those that connect medial temporal and prefrontal cortices) mediated the relationship between fitness and spatial working memory.64 Additional support for the importance of fitness in terms of white matter integrity also exists in pediatric cross-sectional studies, which have found positive associations between fitness and fractional anisotropy in several of the same white matter tracts in children.65

Future Directions
To date, no RCT has examined the impact of a physical activity intervention on volumes of brain regions in children or adolescents. This is surprising given that a recent meta-analysis on the effect of aerobic exercise on hippocampal volume in adults included 14 studies.66 This review revealed a significant effect of aerobic exercise on both left and right hippocampal volume in comparison with control conditions in healthy older adults. The effects were driven by exercise attenuating normal age-related neurodegeneration, which has been shown to precede and lead to cognitive decline and Alzheimer disease.57,68 Whether exercise can increase the volumetric growth of the hippocampus and whether these increases in volume subsequently confer benefits to cognition, memory, and/or academic performance during childhood and adolescence has not been established.

More studies in adolescents are needed because all experimental studies included in this review were conducted with children. Future researchers should also measure cardiorespiratory and muscular fitness so that (1) baseline fitness can be adjusted for in analyses and (2) changes in fitness due to physical activity interventions can be analyzed for correlations with changes in brain structure or function. There is considerable scope for different intensities, frequencies, and types of physical activity such as high-intensity interval training, resistance exercise, exergaming, and cognitively demanding physical activity to be explored.69

Limitations
Although this is the first systematic review of MRI studies in the area of pediatric physical activity, there are some limitations that should be noted. Most notably, because of the small number of RCTs and considerable heterogeneity of included studies, we were unable to conduct meta-analyses. In addition, we did not check for a file drawer effect so the risk of publication bias cannot be ruled out.

There are a number of common study limitations that should be noted. The majority of the included studies included small samples and/or relied on statistical significance analyses. The P values do not provide an indication of the size of an effect nor the importance of a result and by themselves are not a good measure of evidence regarding a model or hypothesis.70 As such, the field needs to progress to promote the reporting of effect estimates in addition to the corresponding statistics.71 Risk of bias was largely unclear across all domains and studies. Researchers are encouraged
to adhere to the Consolidated Standards of Reporting Trials guidelines\textsuperscript{72} to reduce the risk of bias, particularly in terms of selection bias and reporting bias.\textsuperscript{73} Findings need to be interpreted with caution until additional RCTs can (1) replicate findings and (2) establish whether exercise-induced changes in brain structure or function mediate the cognitive and/or academic benefits of physical activity.

**Conclusions**

There is some evidence from RCTs that participation in physical activity may enhance brain structure and function in terms of white matter integrity and activation of regions key to cognitive processes, respectively. No RCT researchers have reported on the impact of physical activity on volumes of brain regions in children or adolescents.

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**ABBREVIATIONS**

ASL: arterial spin labeling  
BDNF: brain-derived neurotrophic factor  
CI: confidence interval  
DTI: diffusion tensor imaging  
fMRI: functional MRI  
HR$_{\text{max}}$: maximum heart rate  
RCT: randomized controlled trial  
VO$_{2\text{max}}$: maximum oxygen consumption

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**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

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Supplemental Information

SUPPLEMENTAL TABLE 4 Search Strategy

<table>
<thead>
<tr>
<th>Search Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>(child* OR adolescent OR youth OR young person OR young people OR school* OR teen* OR preadolescent OR kid* OR development OR maturation)</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>(&quot;physical activity&quot; OR &quot;physical exercise&quot; OR sport OR fitness OR recreation OR walk* OR aerobic activity OR aerobic fitness OR &quot;cardiovascular exercise OR &quot;cardiovascular fitness&quot; OR &quot;cardiorespiratory exercise&quot; OR &quot;cardiorespiratory fitness&quot; OR &quot;VO2&quot; OR &quot;oxygen consumption&quot; OR &quot;aerobic fitness&quot; OR &quot;aerobic capacity&quot; OR &quot;aerobic exercise&quot; OR &quot;muscular fitness&quot; OR &quot;muscular exercise&quot; OR &quot;resistance training&quot;)</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>(brain OR &quot;brain structure&quot; OR &quot;brain function&quot; OR &quot;brain plasticity&quot; OR neurogenesis OR &quot;stem cell&quot; OR MRI OR &quot;magnetic resonance imaging&quot; OR fMRI OR &quot;functional magnetic resonance imaging&quot; OR DTI OR &quot;diffusion tensor imaging&quot; OR BOLD OR &quot;blood oxygen level dependent&quot; OR VBM OR &quot;voxel based morphometry&quot; OR &quot;grey matter&quot; OR &quot;gray matter&quot; OR &quot;white matter integrity&quot; OR volumetry OR &quot;fractional anisotropy&quot; OR &quot;radial diffusivity&quot; OR &quot;resting state&quot; OR &quot;default mode network&quot; OR &quot;spectroscopy&quot;)</td>
</tr>
</tbody>
</table>
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